Local release of dexamethasone from polymer millirods effectively prevents fibrosis after radiofrequency ablation

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Abstract: Recent studies show that after radiofrequency (RF) ablation, fibrosis occurs at the ablation boundary, hindering anticancer drug transport from a locally implanted polymer depot to the ablation margin, where tumors recur. The purpose of this study is to investigate strategies that can effectively deliver dexamethasone (DEX), an anti-inflammatory agent, to prevent fibrosis. Polymer millirods consisting of poly(D,L-lactide-*co*-glycolide) (PLGA) were loaded with either DEX complexed with hydroxypropyl β-cyclodextrin (HPβ-CD), or an NaCl and DEX mixture. *In vitro* release studies show that DEX complexed with HPβ-CD released 95% of the drug after 4 days, compared to 14% from millirods containing NaCl and DEX. Rat livers underwent RF ablation and received either DEX-HPβ-CD-loaded millirods, PLGA millirods with an intraperitoneal (i.p.) DEX injection, or control PLGA millirods alone. After 8 days *in vivo*, heightened inflammation and the appearance of a well-defined fibrous capsule can be observed in both the control experiments and those receiving a DEX injection (0.29 ± 0.08 and 0.26 ± 0.07 mm in thickness, respectively), with minimal inflammation and fibrosis present in livers receiving DEX millirods (0.04 ± 0.01 mm). Results from this study show that local release of DEX prevents fibrosis more effectively than a systemic i.p. injection. © 2005 Wiley Periodicals, Inc. J Biomed Mater Res 76A: 174–182, 2006

Key words: dexamethasone; fibrous capsule formation; inflammation; polymer implant; radiofrequency ablation

INTRODUCTION

Presently, an immense amount of research efforts have been devoted to the development of minimally invasive strategies for the treatment of liver cancers. Chief among the techniques is radiofrequency (RF) ablation, which consists of applying a high-frequency alternating current, that results in tissue destruction by frictional heat.[1] The potential benefits of RF ablation are easily appreciated: complete destruction of the tumor within the ablation radius, short recovery times, and minimal morbidity to the patient. However, local tumor recurrence at the outer periphery of ablation limits its widespread clinical application.[2–4] Hence, many research laboratories have suggested using RF ablation in a multimodality approach for the treatment of tumors, combining the strategy with alternative remedial options such as the systemic delivery of chemotherapeutic drugs[5] and radiotherapy.[6]

In lieu of the above strategies, our laboratory has proposed a combination therapy involving RF ablation and the local delivery of a chemotherapeutic agent. Briefly, the combined strategy involves using RF ablation to destroy the tumor by heat, followed by the implantation of a doxorubicin-loaded polymer millirod at the site of ablation to eliminate residual malignant cells. In our laboratory, research has been carried out in the fabrication and mechanical characterization of drug-loaded polymer millirods,[7] modulation of release characteristics of doxorubicin from the millirods,[8] and study of doxorubicin distribution in liver tissue after RF ablation and subsequent millirod implantation.[9] Previous research by our laboratory has also shown that postablated liver is time variant and that the inflammatory response caused by tissue charring is significant. The result is the forma-

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tion of a thick, well-defined fibrous capsule at the boundary of ablation.[10]

The appearance of a fibrous capsule is widely regarded as favorable and crucial in the walling off of an injurious site during the wound-healing process. However, fibrosis also poses a significant barrier to molecular transport, limiting the clinical acceptance of several implantable biomedical applications. Drug transport hindrance results from the avascularity of the tightly packed collagenous matrix, as well as from the lower diffusion coefficient through the fibrous capsule, arising from the decrease in fluid volume and increase in tortuosity.[11] Altogether, drug released from a polymer depot will reach the tissue immediately beyond the fibrous capsule only in small quantities, because most of the drug will be encapsulated within the implant site.

The local release of dexamethasone (DEX), a potent and synthetic anti-inflammatory glucocorticoid, is being investigated in attempts to prevent fibrosis surrounding devices such as implantable glucose sensors[12] and pacemaker leads.[13] Although several mechanisms are involved in the down-regulation of inflammation after glucocorticoid administration, it is known that DEX blocks the production and secretion of various chemokines, diminishes the release of inflammatory cells to injured sites, and suppresses fibroblast proliferation, ultimately leading to reduced fibrosis.[14] Although the anti-inflammatory advantages of DEX prove appealing, DEX is highly water-insoluble, which proves inconvenient in controlled release applications. Currently, DEX can be complexed with cyclodextrins, which are cyclic oligosaccharides in the form of truncated cones consisting of a hydrophobic core and a hydrophilic outer surface.[15,16] Cyclodextrins have the ability to entrap drug molecules within the hydrophobic core, thereby increasing water solubility and bioavailability of the drug, which in turn can allow for the potentiation of the anti-inflammatory effects of DEX.

The objective of this study is to prevent fibrosis resulting from RF ablation through DEX administration. Millirods composed of poly(D,L-lactide-*co*-glycolide (PLGA) and containing either sodium chloride and DEX or DEX complexed with HPβ-CD, were tested *in vitro* to determine release characteristics. Subsequently, millirods containing DEX complexed with HPβ-CD were examined in an *in vivo* rat model. We hypothesize that the local release of DEX from polymer millirods will effectively prevent fibrous capsule formation at the ablation boundary. To test this hypothesis, RF ablated rat livers received either PLGA control millirods, PLGA control millirods and an intraperitoneal (i.p.) injection of DEX, or a DEX-loaded millirod. Results from this study show that the local release of DEX is effective at preventing fibrous capsule formation after 8 days and more effective at preventing fibrosis than a systemic administration of the drug.

MATERIALS AND METHODS

Materials

PLGA (lactide/glycolide = 1:1; MW 50,000 Da; inherent viscosity 0.65 dL/g) was purchased from Birmingham Polymers, Inc. (Birmingham, AL). Hydroxypropyl β-cyclodextrin (HPβ-CD) was purchased from Cyclodextrin Technologies Development, Inc. (CTD). DEX and DEX-cyclodextrin complex (DEX-HPβ-CD, 70 mg DEX per gram of complex) were purchased from Sigma (St. Louis, MO). Phosphate-buffered saline (PBS; pH 7.4) was purchased from Fisher Scientific (Pittsburgh, PA).

Polymer millirod fabrication and *in vitro* release characterization

Polymer millirods were fabricated by using a previously established compression-heat molding procedure.[7] To summarize, millirod components were weighed separately, placed in a mortar, and well mixed by using a pestle. The contents were inserted into a Teflon tube (1.6 mm I.D.) within a stainless steel mold. The mold was then placed in an oven (Fisher Model 282A) at 90°C for 2 h with a compression pressure of 4.6 MPa. The resulting cylindrical polymer millirod, with a diameter of 1.6 mm, was cut to a length of 8 mm. Millirod Formulation 1 consisted of 24% DEX-HPβ-CD complex (1.7% DEX), 16% HPβ-CD, and 60% PLGA. Formulation 2 consisted of 1.7% DEX, 38.3% NaCl, and 60% PLGA, and control millirods consisted of 100% PLGA.

To characterize the *in vitro* release of DEX-loaded polymer millirods, millirods (n = 3) were placed in a glass scintillation vial that contained 5 mL of PBS at 37°C. A separate study of DEX release from Formulation 2 millirods was conducted in PBS solution containing 1% HPβ-CD. Sample vials were placed in an orbital shaker (C24 model, New Brunswick Scientific) with a rotating speed of 100 rpm. At various time points, the millirod was removed from the solution and placed into a new scintillation vial containing 5 mL of fresh buffer at 37°C. The concentration of released DEX was measured by using a UV-Vis spectrophotometer (Perkin-Elmer Lambda 20 model) at the maximum adsorption wavelength of the drug (λ_{max} = 242 nm). The percentage of cumulative DEX released was obtained by normalizing the released amount to the total amount loaded in the millirods.

Scanning electron microscopy analysis of millirod microstructure

Scanning electron microscopy (SEM) was used to characterize the morphology of DEX-loaded polymer millirods. Millirods were placed in 5 mL of PBS buffer at 37°C for 24 h, after which they were freeze-dried overnight. The millirods were then cut into two parts for both lateral and cross-sectional analysis. A thin film of palladium (Pd; ca. 2 nm in thickness) was sputter-coated to minimize electron charging on the sample surface. A voltage of 5 kV was used during

sample examination with a Hitachi S-4500 scanning electron microscope (Hitachi, Ltd., Japan).

RF ablation of rat livers and millirod implantation

Animal procedures adhered to the National Institutes of Health (NIH) guidelines and followed an approved protocol by the Institutional Animal Care and Use Committee (IACUC) at Case Western Reserve University. Male Sprague-Dawley rats weighing approximately 300 g were anesthetized by using an i.p. injection of sodium pentobarbital. A small midline incision was made, through which the medial lobe of the liver was exposed for RF ablation and millirod implantation. Ablation was induced by using RF-generated current (0.09–0.12 A) from a 19-gauge needle electrode (Radionics®, Burlington, MA) at 90 ± 2°C for 2 min. After the electrode was removed, a millirod was inserted into the electrode tract.

The *in vivo* experiments consisted of three study groups (n = 4). The first group received control millirods composed completely of PLGA. The second group also received a control PLGA millirod, as well as a 1-mL i.p. injection of DEX-HPβ-CD complex in saline (1.25 mg of DEX-HPβ-CD/kg). The third group consisted of animals that received a DEX-releasing implant (Formulation 1).

Histological analysis of ablated livers

At 4- and 8-day time points, animals were sacrificed, livers were removed, and polymer millirods were retrieved. After the liver was sectioned, it was fixed in 10% formalin solution, embedded in paraffin, and sliced to a thickness of 5 μm. Samples were stained with hematoxylin and eosin (H&E) and Masson's trichrome (MTC) stains. The H&E stain provided for appreciation of cellular detail, whereas the MTC stain facilitated the examination of collagen fibers (stained blue) and overall fibrous capsule formation. Histological images were taken by using a Nikon Eclipse TE300 microscope with a SPOT RT Slider camera. Masson's trichrome stained samples (n = 3) were used in quantifying the thickness of the fibrous capsule, with measurements obtained by averaging from eight radial directions around the ablation boundary. Statistical analysis between groups consisted of two-tailed *t*-tests of unequal variances, with a significance level of 0.05.

RESULTS

In vitro release of DEX from polymer millirods

The *in vitro* release characteristics of DEX from polymer millirods of two different formulations are shown in Figure 1. In Formulation 1, the DEX is complexed with HPβ-CD, whereas in Formulation 2, DEX is uncomplexed in the presence of a salt excipient. Both formulations contain the same loading percentage of DEX (1.7% or 0.5 mg per implant), with differences in release characteristics stemming from whether the DEX is complexed with cyclodextrin.

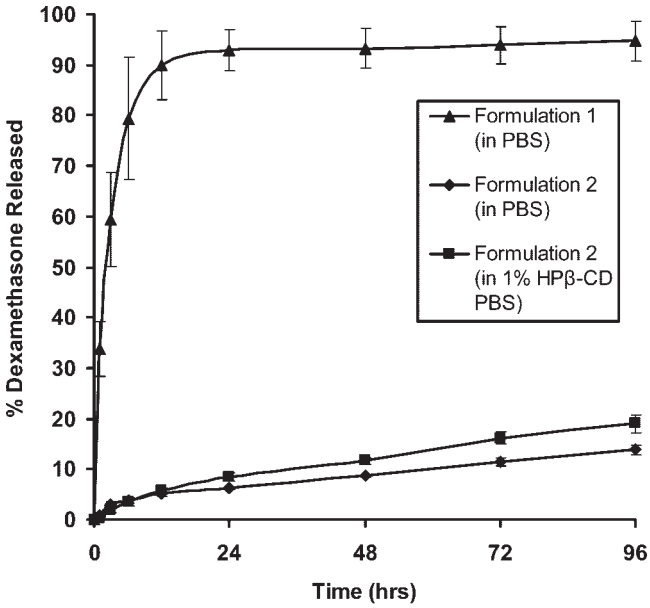

Figure 1. *In vitro* release profiles of DEX-loaded millirods of varying formulations. Formulation 1 is composed of 60% PLGA, 16% HPβ-CD, and 24% DEX complexed with HPβ-CD (1.7% total DEX). Formulation 2 is composed of 60% PLGA, 38.3% NaCl, and 1.7% uncomplexed DEX. The error bars were calculated from triplicate samples.

Data show that the release of DEX from polymer millirods pertaining to Formulation 1 is much faster than that from Formulation 2. After 6 h, approximately 80% DEX has been released when the drug is complexed with HPβ-CD, whereas only 4% release was observed with millirods pertaining to Formulation 2 at the same time point. Four days into the release study, approximately 95% of the drug has been released from Formulation 1, whereas the percentage of cumulative release from Formulation 2 has only reached roughly 14%. To determine the solubilization effect of cyclodextrin on the release kinetics of dexamethasone, a release study was conducted in PBS containing 1% HPβ-CD. Figure 1 shows that the release of DEX in PBS containing 1% HPβ-CD is similar to that in regular PBS, with approximately 19% of the drug released after 96 h. Given the faster release of DEX from Formulation 1, millirods composed of 24% DEX-HPβ-CD complex, 16% HPβ-CD, and 60% PLGA were used in subsequent animal experiments.

SEM analyses of DEX-loaded millirods

To further examine the disparity in DEX release from two different formulations, SEM analyses were

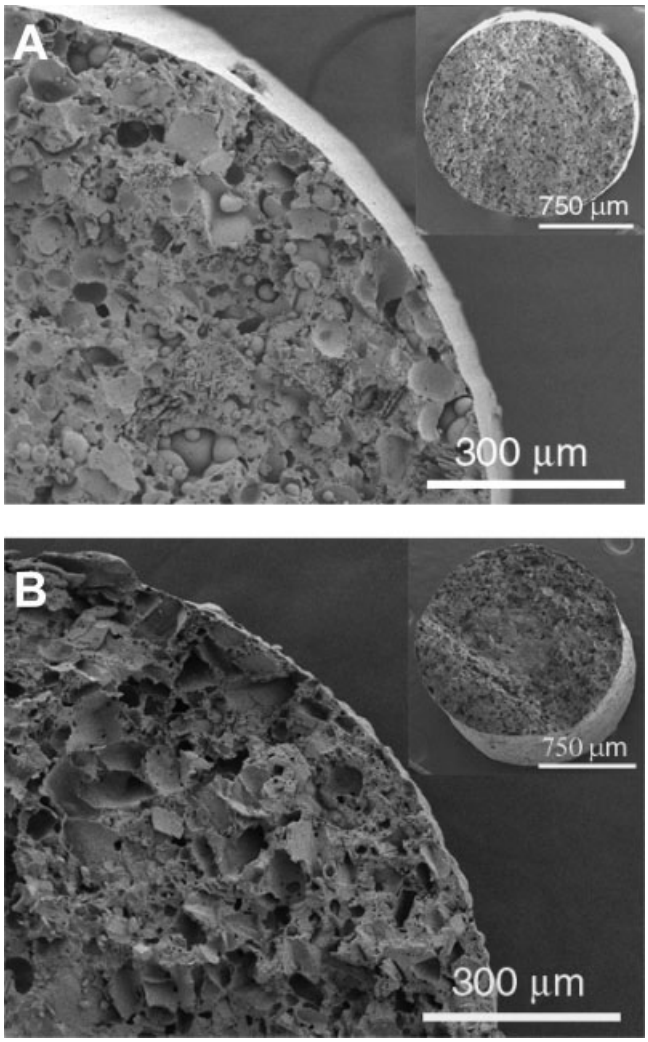

Figure 2. SEM analysis of polymer millirod microstructure after 24-h immersion in PBS buffer. (A) A magnified image of the cross section of a millirod pertaining to Formulation 1. (B) A cross-sectional magnification of a millirod from Formulation 2. The insets in (A) and (B) represent low-magnification images of the cross sections of the respective millirods.

performed on millirods that had been immersed in PBS for 24 h. Figure 2(A,B) represents cross-sectional images of millirod from Formulations 1 and 2, respectively. Closer examination reveals that the pores in Formulation 1 are spherical, whereas the pores in Formulation 2 are polyhedral, reflecting the original shapes of salt crystals within the polymer matrix. As can be observed from the figure insets, the two millirod formulations are morphologically similar, with comparable porosity throughout the millirod cross sections.

Fibrous capsule formation after RF ablation and millirod implantation

Four days after RF ablation, the inflammatory response remains in its early stages, and although collagen deposition exists at the ablation boundary, extensive fibrous capsule formation has not yet occurred. A thin layer of blue-staining collagen fibers is present to a moderate degree at the ablation boundary in livers receiving a PLGA control millirod, heralding the initiation of fibrous capsule formation (data not shown). A similar pattern of collagen deposition can be observed in RF ablated livers that received a PLGA millirod and an i.p. injection of DEX. Negligible amounts of collagen deposition were observed in liver samples that received DEX-loaded millirod implants.

Eight days after RF ablation, one can observe the formation of a thick, well-defined fibrous capsule at the ablation boundary, easily discernable in Figure 3(A). A dense, collagen-rich layer exists at the ablation boundary separating the ablated and nonablated regions. The pattern of fibrous capsule formation in animals receiving a PLGA millirod and an i.p. injection of DEX mimics that of the control experiments, and this is evident in Figure 3(B). As in the control experiment, there is a dense fibrous capsule present at the ablation boundary, evidenced by the substantial amount of blue-staining collagen fibers. These figures show that i.p. injected DEX has minimal effect on prevention of fibrosis. When liver samples undergo RF ablation and the implantation of a DEX-loaded millirod, minimal fibrosis is present. As can be seen in Figure 3(C), only minute amounts of collagen fibers are present at the ablation boundary. A distinct boundary separates the ablated and nonablated regions.

Fibrous capsule thickness 4 and 8 days after ablation

Although histological examination of ablated liver samples provided for qualitative insight into the extent of fibrous capsule formation, a quantitative comparison displaying disparities in fibrosis among the experimental groups is shown in Figure 4. The similarity in fibrous capsule formation after 4 days between ablated livers receiving DEX as an injection and ablated livers receiving no DEX is further highlighted by the equivalent thickness measurements at the 4-day time point, with both groups containing a layer of fibrosis measuring 0.13 ± 0.01 mm. The quantitative measurement of fibrous capsule thickness in animal livers receiving DEX-loaded millirods, 0.02 ± 0.01 mm, confirms the minimal fibrosis visible after 4 days. The calculated p-value ($p < 10^{-5}$) shows a statistical significance when comparing the DEX-loaded millirod sample to the control sample.

Eight days after RF ablation and millirod implantation, histological analysis shows the presence of a dense, well-formed fibrous capsule at the ablation

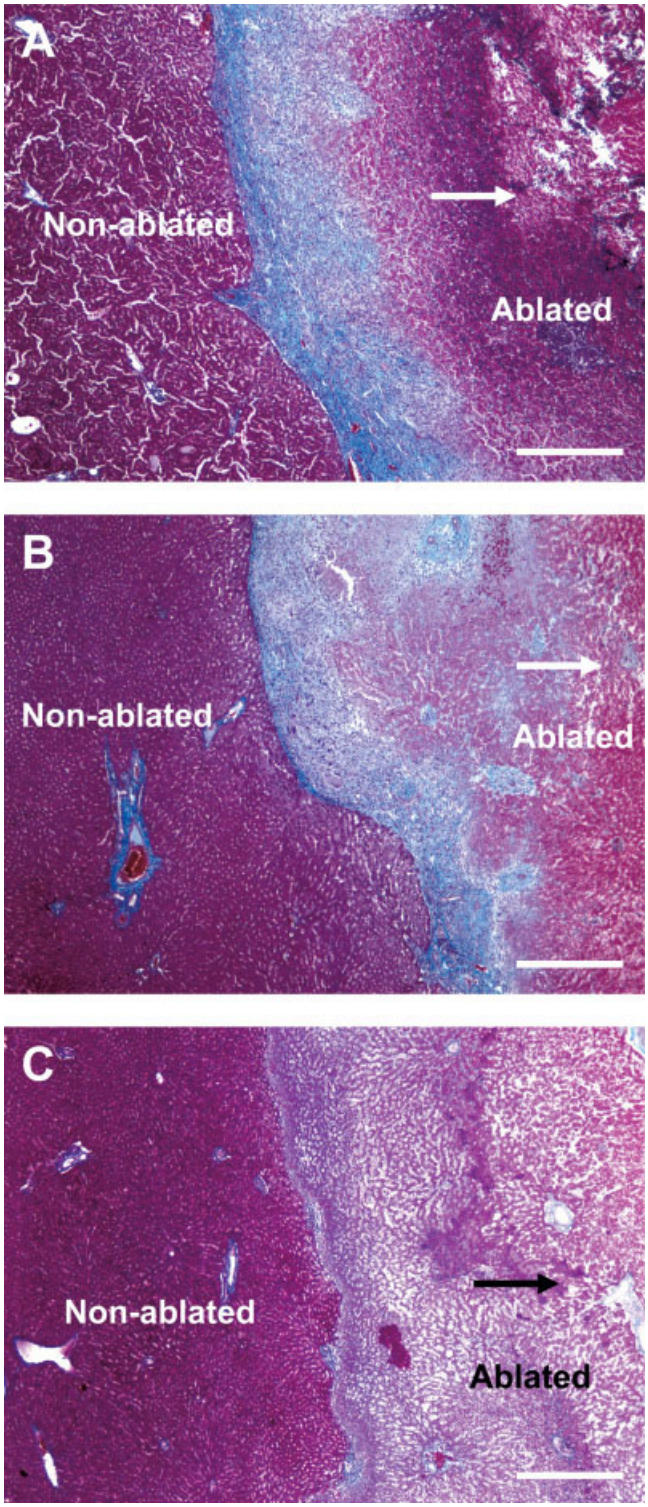

Figure 3. Histology images of liver samples 8 days after RF ablation and millirod implantation (all MTC stained; original magnification ×4). (A) Postablated liver receiving a control PLGA millirod. (B) A sample that received a PLGA millirod and an i.p. injection of DEX. (C) Ablated liver that received a DEX-loaded millirod. The arrow points in the direction of the site of liver ablation/millirod implantation. The scale bars in the images = 0.5 mm. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

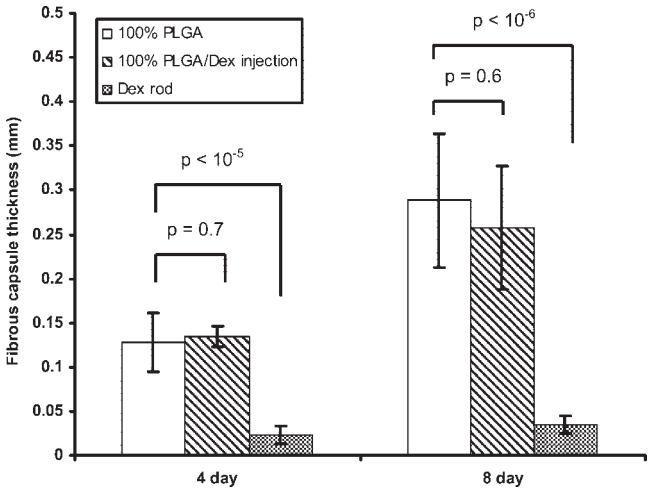

Figure 4. Measurements of fibrous capsule thickness in liver samples 4 and 8 days after RF ablation and millirod implantation in three different animal groups. The *p*-values are shown to highlight statistical differences between the groups.

boundary. In ablated liver samples receiving control millirods, extensive fibrosis measuring 0.29 ± 0.08 mm occurs after 8 days, which is twice the thickness measured at the 4-day time point. The average fibrous capsule thickness measurement in ablated livers receiving a PLGA millirod and an i.p. DEX injection was 0.26 ± 0.07 mm, further confirming the inefficacy of the DEX injection in preventing fibrosis. On the other hand, ablated liver samples receiving a DEX-loaded millirod had minimal collagen deposition and the absence of a fibrous capsule at the 8-day time point, with the average thickness measurement being 0.04 ± 0.01 mm. As in the 4-day time point, the *p*-value ($p < 10^{-6}$) shows statistical significance between control samples and livers receiving DEX-loaded millirods.

Inflammatory response at the ablation boundary after RF ablation

Fibrous capsule formation represents one of the most distinguishable characteristics of the inflammatory response, arising from processes such as leukocyte extravasation to the injured site and fibroblast migration. In an attempt to discern the prevalence of inflammatory processes that might give rise to fibrosis, H&E histology was compared for each of the animal groups at 4- and 8-day time points. The inflammatory response at the ablation boundary is in the acute phase 4 days after ablation, with most cells in the region consisting primarily of monocytes (data not shown). A similar inflammatory response was observed in RF-ablated liver samples that received an i.p. DEX injection. In sharp contrast to the acute inflam-

matory response observed in the previous animal groups, ablated livers receiving a DEX-loaded millirod showed no signs of inflammation.

By the 8-day time point, the inflammatory response has progressed and yielded the formation of a thick fibrous capsule. Now in the chronic inflammatory stage, a greater number of inflammatory cells, mainly macrophages, can be found at the ablation boundary[17] [Fig. 5(A)]. Also apparent from the figure is the heightened number of fibroblasts, aligned circumferentially around the ablation tract, and the presence of new blood vessels, another hallmark of wound healing. Rat livers that received PLGA millirod implants and an i.p. injection of DEX show the same extent of inflammation as controls after 8 days, as evidenced by Figure 5(B). After DEX-loaded polymer millirod implantation, the inflammatory response at the ablation boundary is minimal after 8 days [Fig. 5(C)]. Negligible amounts of inflammatory cells and fibroblasts can be observed, explaining the lack of collagen deposition at this time point.

DISCUSSION

The objective of this study was to prevent fibrous capsule formation after RF ablation through the local release of DEX. Results from the study show that a site-specific, local release of DEX complexed with HPβ-CD was effective in preventing fibrous capsule formation up to 8 days.

Complexing DEX with HPβ-CD facilitates DEX delivery

The cascade of events leading to fibrous capsule formation occurs rapidly after the charring event produced by RF ablation. The rapidity of the inflammatory response warrants a fast release of DEX to counter the extravasation of neutrophils and monocytes to the site of injury, which would otherwise initiate fibroblast migration to the ablation boundary.[12] Results from this study show that DEX complexed with cyclodextrin (Formulation 1) releases much faster from polymer millirods than uncomplexed DEX (Formulation 2).

One potential explanation for the faster release of DEX from Formulation 1 could be the increased water solubility of the otherwise water-insoluble DEX when it complexes with HPβ-CD. DEX has a solubility in water of 0.1 mg/mL,[18] whereas DEX-HPβ-CD has a solubility of 25 mg/mL, an elevated solubility that would create a higher concentration gradient for faster release. If the slow release of the drug is indeed a

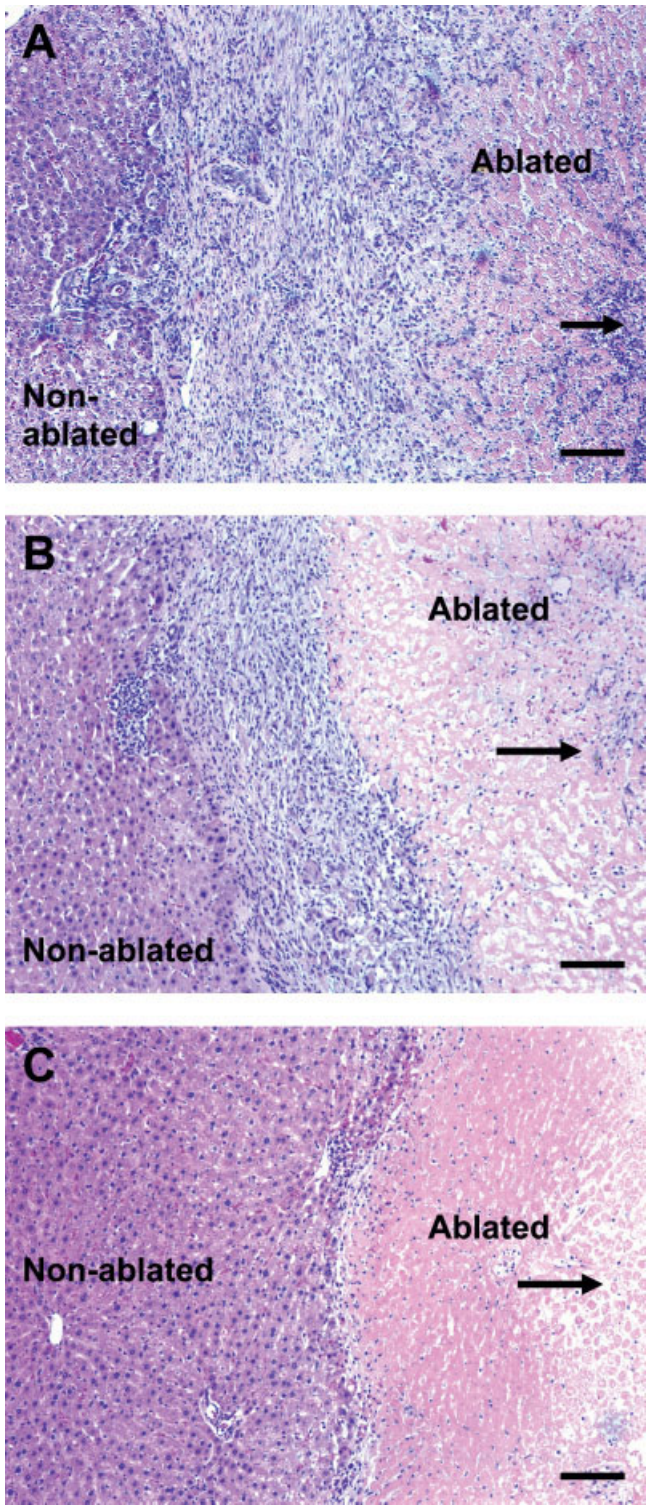

Figure 5. Histological representation of liver samples 8 days after RF ablation and millirod implantation (all H&E stained; original magnification × 10). (A) A control liver sample receiving a PLGA millirod. (B) A sample that received a PLGA millirod and an i.p. injection of DEX. (C) Ablated liver that received a DEX-loaded millirod. The arrow points in the direction of the site of liver ablation/millirod implantation. The scale bars in the images = 0.1 mm. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

solubility issue, then the release of DEX from Formulation 2 in PBS solution containing 1% HPβ-CD would have been much faster and would have approximated the release of millirods containing DEX-HPβ-CD. However, the release of DEX is akin to that of Formulation 2 in regular PBS solution. On qualitative examination of the millirod microstructure with SEM, it was also found that the faster release of DEX was not due to an increase in the presence and size of pores in the polymer matrix. Morphologically, both formulations are comparable in terms of porosity, excluding differences in tortuosity as a cause for the discrepancies in release kinetics.

In light of these findings, the most likely explanation for the slow release of DEX from Formulation 2 millirods is the dissolution of DEX in PLGA matrix. During the annealing process at 90°C, the hydrophobic drug dissolves in the hydrophobic PLGA, leading to a molecular-level mixture with much slower release of the drug. Panyam et al.[19] observed this phenomenon in DEX-releasing PLGA nanoparticles and noted that the solid-state solubility of DEX exists up to 6.7%, considerably higher than the DEX loading in these millirods. The faster release of the drug from Formulation 1 can best be explained by the fact that DEX is encapsulated within the core of the cyclodextrin, which in turn prevents drug dissolution in the polymer. The faster release and heightened bioavailability of the drug provided by millirods containing DEX complexed with HPβ-CD resulted in the use of these millirods in thermoablated rat livers, in hopes of preventing the early onset of wound healing.

Locally released DEX from polymer implant prevents fibrosis

Previous studies showed that ablated liver tissue undergoes wound-healing processes, such as inflammatory cell extravasation, fibroblast migration, and collagen secretion, which eventually culminate in fibrosis. This leads to the presence of various different zones in postablated liver, composed of a zone of viable hepatocytes, a region of fibrosis, an area of cellular debris, a zone of migratory inflammatory cells, and a necrotic core. In this study, through the local delivery of water-soluble DEX from a polymer millirod implanted at the ablation site, postablated liver tissue did not undergo inflammation 8 days after ablation. Inflammatory processes, such as cellular migration and collagen deposition, were found only to a minimal degree, and no signs of fibrous capsule formation were evident. This resulted in the presence of two zones in postablated liver: an ablated, necrotic region and a nonablated region consisting of viable hepatocytes.

Systemic administration of glucocorticoids for the management of highly localized inflammatory states proves disadvantageous because of harmful side effects (e.g., hypertension, increased susceptibility to infection), as well as the failure to achieve adequately high drug concentrations at the intended site of action.[20] For our purposes, we want to prevent fibrous capsule formation at the boundary of ablation, with the hypothesis being that a local controlled release of DEX from a polymer millirod at the ablation site would be more effective than a systemic (intraperitoneal) injection of the drug. The results from this study show that in RF-ablated livers receiving a systemic DEX injection, fibrous capsule formation is similar to that in control-ablated livers. Inflammatory processes, including fibroblast migration and collagen deposition, can be seen to the same degree in both animal groups, yielding fibrous capsule thicknesses whose difference is not statistically significant at 4 and 8 days. Contrary to these results, DEX released locally at the site of ablation was able to prevent fibrosis up to 8 days after RF ablation, with negligible wound healing. The disparity in fibrosis between the systemic administration of DEX and the local delivery of the drug arises from the fact that the tissue immediately surrounding the injured site is exposed to higher doses of the drugs for longer periods of time when the administration is site-specific. The one-time systemic administration of DEX is rapidly cleared by the body, and the ablated region is not exposed to adequate levels of DEX.

Implications for intratumoral drug delivery

Previous work by our laboratory led to the development of a combination therapy for the treatment of liver cancer that involves destroying the tumor by RF ablation, followed by the implantation of a doxorubicin-loaded polymer millirod to eliminate recurrent malignant cells at the outer margin.[7] Detrimental to the success of the combination therapy is the formation of a thick, well-defined fibrous capsule at the boundary of ablation that hinders drug transport past the ablated region.[10] The intricate architecture of the fibrous capsule consists of tightly packed collagen fibers that give rise to a highly tortuous matrix with minimal fluid volume, which encapsulates most of the drug within the ablated region. Thus, arresting fibrous capsule formation after RF ablation through the local release of DEX should prove beneficial for intratumoral drug delivery.

Fibrous capsule formation, however, is not the only inflammatory process that can interfere with drug transport to the intended site of action. An essential component of the wound-healing process is the for-

mation of new blood vessels, occurring at later stages of inflammation, parallel with fibrosis. Several growth factors associated with wound healing contribute to angiogenesis, with vascular endothelial growth factor (VEGF) playing an important role.[21] In the results obtained in this study, new blood vessel formation was shown to occur at the boundary of ablation (within the granulation tissue) in control livers 8 days after ablation. Contrary to these results, ablated livers receiving DEX polymer millirods showed no signs of angiogenesis at the ablation boundary. Angiogenesis at the ablation boundary can act in an unfavorable fashion, mainly because the new blood vessels increase local drug clearance. In numerous studies, DEX has been shown to exhibit antiangiogenic effects.[22,23] Hence, the local release of DEX may enhance the effects of the intratumorally delivered chemotherapeutic agent.

Because DEX is an anti-inflammatory agent, it may also aid in preventing tumor recurrence at the ablation boundary. It is well known that an inflammatory state is critical for tumor potentiation. In and around a developing tumor, inflammatory cells secrete growth factors that in turn promote angiogenesis and remodel the extracellular matrix to facilitate metastasis.[24,25] Fibroblasts and infiltrating inflammatory cells, such as monocytes/macrophages, granulocytes, and mast cells, produce enzymes, chemokines, and cytokines that are mitogenic for the tumor.[26] Postablated liver tissue exists in a highly inflammatory state, especially at the boundary of ablation, which may help explain the propensity for tumor recurrence. In light of the causal relationship between inflammation and tumor recurrence, Harrison et al.[27] suggested targeting the postinflammatory state as a potential follow-up to RF ablation to prevent tumor recurrence. In this study, we have shown that the local release of DEX was able to prevent inflammation at the ablation boundary. This deterrence of inflammation after RF ablation may potentially help decrease the risk of locoregional tumor recurrence.

CONCLUSIONS

Results from this study show that local delivery of DEX, complexed with HPβ-CD and released from a polymer millirod after RF ablation, is capable of preventing fibrous capsule formation. Compared with ablated livers receiving a systemic DEX injection, livers receiving DEX-loaded polymer implants showed minimal inflammation and fibrosis. Future studies will focus on designing polymer millirods that release an anticancer agent concomitantly with DEX, in hopes that the anti-inflammatory effects of DEX will enhance drug transport and efficacy in tumor treatment.

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